

REMARKS

Claims 37-72 were rejected, and claims 1-18 and 25-36 were withdrawn from consideration. Applicants have herein amended claims 37, 52, 53, 70 and 71 to recite that the dummy atom(s) has/have a positive charge. Support for the amendments can be found throughout the specification, including at paragraphs [0030], [0031], and [0037] of US 2004/0148149, the U.S. publication of the above-referenced application. In particular, paragraph [0031] states that a “tetrahedral zinc molecule having a tetrahedral configuration has five atoms. One atom is assigned the total size of the molecule, i.e., the center atom The center atom is not assigned a charge. The remaining four atoms are covalently bonded to the center atom and are referred to as dummy atoms. . . . The dummy atoms do, however, carry a charge. In particular, it is advantageous to assign a fraction of the total charge of the ion to each dummy atom. . . . For example, in a tetrahedral zinc molecule having a total charge of +2, each dummy can be assigned a +0.5 charge.” Applicants respectfully assert that one having ordinary skill in the art would therefore understand that the dummy atom(s) is/are assigned some or all of the total positive charge on the metal ion that is being modeled to have a particular polyhedral configuration. Accordingly, no new matter has been added.

Applicants have herein amended claims 42 and 60 to recite that the group of polyhedrons consists of tetradedrons, trigonal bipyramids, square pyramids and octahedrons. Support for the amendments can be found within the specification, including at paragraph [0052], where the present inventor notes that “[t]he tetrahedral geometry of a conventional zinc ion was converted to a trigonal bipyramid” during a molecular modeling simulation. Additional support for the amendments can be found in Alberts *et al.* [Protein Science, vol. 7, 1998, pages 1700-1716], incorporated by reference in its entirety in the present application. *See* paragraph [0018]; Alberts *et al.* at 1702 tbl. 1A, 1704 & fig. 2, 1707 tbl. 3B. Applicants respectfully assert that one having ordinary skill in the art would therefore understand that the group of polyhedrons listed in the claim are commonly known coordination geometries of metal ions. Accordingly, no new matter has been added.

Upon entry of these amendments, claims 37-72 remain pending, with claims 1-18 and 25-36 withdrawn from consideration. In light of the amendments and remarks herein, Applicants respectfully request reconsideration and allowance of the pending claims.

Rejections under 35 U.S.C. § 112

In the Office Action mailed January 17, 2007, claims 52, 53, 70 and 71 were rejected as indefinite for listing values of charge without assigning a sign (negative or positive) to the value. In the Advisory Action mailed March 28, 2007, Applicants overcame those rejections by amending the claims by indicating that the charge could be either positive or negative. Applicants have herein amended claims 37, 52, 53, 70 and 71 to clarify that the dummy atom(s) has/have solely a positive charge. As described above, no new matter has been added, and Applicants therefore request that the amendments be entered.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 37-47, 49-65, and 67-72 under 35 U.S.C. § 103(a) as being unpatentable over the Huheey *et al.* Inorganic Chemistry textbook ("Huheey") in view of a Journal of Physics article by Marchi *et al.* ("Marchi"), as evidenced by a lecture on Transition Metal/Coordination Chemistry by Crawford ("Crawford"). In particular, Examiner relies on crystal field theory as the basis of rejection. The Examiner stated:

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the crystal field theory discussed in Huheey *et al.* as evidenced by the definition of ligand of Crawford in view of the computer molecular dynamic simulations of Marchi *et al.*, because Marchi *et al.* conducts simulations and measurements on analogous metal ion complexes than those discussed in Huheey *et al.* with the advantages of computer automation and analysis of the energetics of a solvent with the metal in solution to study the properties of alkali atoms (Li, Na, Cs) immersed in liquid ammonia.
See Office Action at 6.

Applicants respectfully traverse on the grounds that the Office has failed to establish a *prima facie* case of obviousness. In particular, the Office has misconstrued the application of crystal field theory to the present invention. Thus, the Office has failed to articulate a reason having a rational underpinning as to why the present claims are obvious given the cited art.

As the Supreme Court recently clarified, for an invention to be obvious under § 103 requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. Moreover, an explicit rationale for why one having ordinary skill in the art would have combined the elements in the manner claimed must be set forth. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ____ (2007), 2007 WL 1237837 (hereinafter “KSR”). Indeed, “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness” *Id.* at 14 (quoting *In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006)).

The present disclosure relates to molecular dynamics simulations of metalloproteins, where the structure of a positive polyhedral metal *ion* is replicated by situating partial positively-charged dummy atoms around a neutral central atom having the van der Waals radius of the metal ion. The dummy atoms are fixed in the position where the positive metal ion's vacant electronic orbitals otherwise reside. *See* paragraph [0006]. Essentially, the metal ion's positive charge is divided among the dummy atoms, which are fixed in space around the central atom, to preserve the metal ion's polyhedral structure (*e.g.*, as evidenced by crystal structures) in the course of modeling.

Huheey discloses crystal field theory as applied to transition metal *compounds*, compounds which are composed of an ion and various “ligands” bonded thereto, where the compound's ligands interact with the central metal ion's *d*-orbitals, causing degeneracy. *See* Huheey at 397-98, 401-03, 408-12. The “ligands” utilized in crystal field theory are compounds distinct from the central metal ion. Huheey lists examples of such ligands, including ammonia, cyanide, and water. *See* Huheey at 408, Table 11.7. It is important to note that the ligands referred to in crystal field theory are ligands that bind a central metal ion in a particular orientation and bear *negative* charges or are electron rich. The negative charges or electron density of the ligands interact with the electron-poor (*e.g.*, positively charged) *d*-orbitals of the metal ion to result in a complex having a particular polyhedral orientation. *See, e.g.*, Huheey at

398 n.16. Moreover, and importantly, crystal field theory is a bonding model that fixes the ligands of a complex in a particular geometry. *See* Huheey at 408-09.

The present disclosure, on the other hand, is directed towards modeling a transition metal ion in a polyhedral orientation and does not involve “ligands” as they are understood in crystal field theory. The present disclosure models a positive metal ion in a particular polyhedral orientation by assigning all of the size of the metal ion to a central atom and dividing the ion’s positive charge among dummy atoms fixed in a particular polyhedral orientation around the central atom via a covalent bond to the central atom. *See* paragraphs [0031] & [0033]. The dummy atoms utilized in the present molecular dynamics simulation are distinct from and clearly not the “ligands” described in Huheey. Whereas the ligands described in Huheey involve discrete atoms or molecules (e.g., ammonia, water, cyanide) unrelated to the metal atom, the dummy atoms presently claimed are not discrete atoms or molecules at all—they merely constitute a positive charge component of the metal ion. The dummy atoms are assigned a small mass in order to create a covalent bond to the central atom, thereby preserving the polyhedral structure of the metal ion. *See* paragraphs [0014], [0031] & [0033]. Thus, the dummy atoms individually represent partial-*positive* point charges, that, when taken together, account for the overall charge of the metal ion.

Moreover, whereas the ligands in crystal field theory are fixed as point negative charges in a particular orientation around a metal ion, the present invention’s metalloprotein ligands (e.g., amino acid side chains or solvent molecules) are not fixed, but indeed are allowed to move about the metal ion during the modeling simulation. *See* paragraph [0004], [0006] & [0007] (“The method . . . enables a researcher to . . . simulate the metal ion’s polyhedral complex, and simulate the *exchange* of ambidentate ligands of the metal ion coordination complex in proteins.”).

Thus, Examiner’s reliance on the crystal field theory is misplaced. The Examiner stated:

Figure 11.6 on page 397 of Huheey *et al.* illustrates the model of crystal field theory for a monoatomic metal with a finite radius and black ligands. . . . The ligands fit the criteria for mass and charge for “dummy atoms,” as stated in the instant claims. . . . Huheey *et al.* uses the term “ligands” instead of “dummy atoms.”

See Office Action at 4-5.

However, as would be clear to one having ordinary skill in the art, the partial-positive point charges of the central metal ion, as presently disclosed, are not the negative point charges, or ligands, envisioned by crystal field theory as described in Huheey. Thus, there is a clear gap in content between the present claims and the disclosure of Huheey, as Huheey is silent as to the apportioning of a metal ion's positive charge to dummy atoms arranged in a particular orientation around a metal ion.

Crawford's lecture on crystal field theory likewise is inapplicable to the present invention, and does not cure the deficiencies of Huheey. Crawford states that the crystal field theory "treats ligands as point negative charges" and "assumes ionic bonding between the metal and the ligands." *See* Crawford at slide 39 of 60. As discussed above, Applicants treat the dummy atoms *not* as ligands having point negative charges, but as partial-positive point charges. Moreover, unlike ligands, the dummy atoms play no role in bonding the metal ion to any other compound. *See* paragraph [0006] ("the dummy atom may not have van der Waals interactions with other atoms"). The present invention utilizes the dummy atoms that embody the metal ion's charge to preserve the metal ion's polyhedral orientation in modeling because molecular modeling programs otherwise distort that orientation when the metal ion's charge is assigned the same location as the metal ion's van der Waals radius. *See* paragraphs [0026] & [0033]. Thus, Crawford does not fill the clear gap in content between Huheey's basic discussion of crystal field theory and the present invention.

Likewise, Marchi is inapposite to the presently claimed invention. Marchi discusses molecular dynamics simulations on compositions of alkali ions and ammonia. *See* Marchi at 5836. Examiner states that Marchi "conducts simulations and measurements on analogous metal ion complexes than those discussed in Huheey *et al.* . . . to study the properties of alkali atoms (Li, Na, Cs) immersed in liquid ammonia. *See* Office Action at 6. Examiner further states that "the ammonia ligands to the alkali ions discussed in this study are series of point charges, which aid in describing the instant claim." *See* Advisory Action at 2. However, as discussed above, Applicants' modeling method does not use "ligands" such as ammonia. Consequently, the simulations described in Marchi are inapplicable because Marchi's simulations involve a metal

atom interacting with negatively charged ligands, whereas the present invention models a metal ion with partial-positive point charges.

Taken together, Huheey, Crawford and Marchi do not support a case of obviousness because they would not prompt one skilled in the art to fix partial-positive dummy atoms around a central, charge-free atom in order to model a metal ion. Crystal field theory is silent regarding modeling of a metal ion *per se*, by, *e.g.*, apportioning the metal ion's positive charge.

Accordingly, Applicants respectfully assert that the claims 37-47, 49-65, and 67-72 are not obvious, and request withdrawal of the rejections under 35 U.S.C. § 103.

The Examiner also rejected claims 37, 48, 55 and 66 under 35 U.S.C. § 103(a) as being unpatentable over Huheey as evidenced by Crawford in view of Marchi as applied to claims 37-47, 49-65 and 67-72 above, and further in view of Maggiora's article in the Journal of the American Chemical Society ("Maggiora"). The Examiner stated:

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify Huheey *et al.* as evidenced by Crawford in view of Marchi as applied to claims 37-47, 49-65, and 67-72 above in further view of Maggiora because Maggiora shows how magnesium can possess d orbitals useful in the crystal field theory for binding the ligands (dummy atoms). Consequently, it would have been obvious for magnesium to be included in the ions disclosed in Huheey *et al.*
See Office Action at 7.

Applicants respectfully request these rejections be withdrawn for the same reasons as discussed above regarding claims 37-47, 49-65, and 67-72, *e.g.*, the inappropriate application of crystal field theory to the present claims. Maggiora discloses nothing that would prompt one having ordinary skill in the art to modify the disclosures of Huheey, Crawford, and/or Marchi so dramatically as to alter crystal field theory's treatment of ligands as fixed point negative charges to result in the assignation of a positive metal ion's size to a central atom and the apportionment of the positive charge to dummy atoms arranged in a particular orientation around a central atom, as presently claimed.

Accordingly, Applicants respectfully assert that the claims are not obvious under 35 U.S.C. § 103 and respectfully request withdrawal of the rejections.

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CONCLUSION

Applicants respectfully assert that the present claims are in condition for allowance, which action is hereby requested. The Examiner is invited to telephone the under-signed attorney if such would expedite prosecution.

Please charge Deposit Account 06-1050 in the amount of \$395 for the Request for Continued Examination fee. Please apply any other charges or credits to Deposit Account 06-1050.

Respectfully submitted,

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